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The EAN COVID-19 registry (ENERGY): An international instrument for surveillance of neurological complications in patients with COVID-19

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Abstract

The COVID-19 pandemic is a global public health issue. Neurological complications have been reported in up to one-third of affected cases, but their distribution varies significantly in terms of prevalence, incidence and phenotypical characteristics. Variability can be mostly explained by the differing sources of cases (hospital vs. community-based), the accuracy of the diagnostic approach, and the interpretation of the patients' complaints. Moreover, after recovering, patients can still experience neurological symptoms. To obtain a more precise picture of the neurological manifestations and outcome of the COVID-19 infection, an international registry (ENERGY) has been created by the European Academy of Neurology (EAN) in collaboration with European national neurological societies and the Neurocritical Care Society and Research Network (NCRN). ENERGY can be implemented as a stand-alone instrument for patients with suspected or confirmed COVID-19 patients AND neurological findings or as *an addendum* to an existing registry not targeting neurologic symptoms. Data are also collected to study the impact of neurological symptoms and neurological complications on outcomes. The variables included in the registry have been selected in the interest of most countries, to favour pooling with data from other sources, and to facilitate data collection even in resource-poor countries. Included are adults with suspected or confirmed COVID-19 infection, ascertained through neurological consultation, and providing informed consent. Key demographic and clinical findings are collected at registration. Patients are followed up to 12 months in search of incident neurological manifestations. As of August 19, 254 centres from 69 countries and four continents have made requests to join the study.

Key words: COVID-19, SARS-CoV-2, neurological diseases, complications, outcome, registry, EAN.

Historical background and rationale

The present pandemic attributed to SARS-CoV-2 virus has become a global public health problem (https://covid19.who.int). This highly contagious coronavirus (more than 21 million people resulting positive, as of August 17), is responsible in humans of different expression of infection severity and

involvement of organs/systems, including the nervous system [Wiersinga et al, 2020]. Neurotropism is a common feature of coronaviruses [Wu et al, 2020] and can be due to a direct action on the nervous tissue and/or to an indirect action through the activation of cytokine cascade and immune-mediated mechanisms [Michalikova et al, 2017; Zubair et al, 2020; Cheng et al. 2020]. Additionally, neurological symptoms can occur as a complication secondary to systemic illnesses or from the exacerbation of pre-existing neurological conditions. Neurological manifestations include symptoms reflecting the overall severity of the disease (as documented by encephalitis and encephalopathy) or more specific syndromic entities (e.g., stroke or Guillain-Barre syndrome) that might be the result of the peculiar mechanisms of action of the virus [Romero-Sanchez et al, 2020].

Neurological manifestations have been reported in about one-third of adult and elderly cases, as indicated in the first clinical series from Wuhan, China [Mao et al, 2020]. Children have also been shown to be affected, although to a lower extent [Garazzino et al, 2020]. Data are mostly driven by case reports and small series that are illustrated in a comprehensive review [Ellul et al, 2020]. Headache, myalgia, anosmia, fatigue/sleepiness are the most frequently reported symptoms [Moro et al, 2020]. Among severe manifestations, altered mental status [Varatharaj et al, 2020], stroke [Divani et al, 2020; Tan et al, 2020] and peripheral nerve involvement [Galassi & Marchioni, 2020] can be the most frequent. Mild complaints and subclinical findings are not uncommon and might indicate that neurological findings are more common than expected and are underdiagnosed unless accurate screening methods are adopted. This suggests that an active search might be followed by even higher numbers. Moreover, it is becoming evident that several symptoms persist after recovering from COVID-19 infection [Carfì et al, 2020]. This new evidence suggests further and careful surveillance and monitoring.

In published reports, the distribution of neurological symptoms, signs and diseases varied significantly in terms of prevalence, incidence and phenotypical characteristics. This variability can be mostly explained by the differing sources of cases (hospital vs. community-based), the accuracy of the diagnostic approach, and the subjective interpretation of the patients' complaints by the attending physicians. Thus, a standardised approach is needed to provide a clearer outline of the spectrum of neurological disorders comparing the main clinical aspects of COVID-19 disease in different countries and verify whether differences, if any, could be attributed to differences in environmental and genetic factors. The approach also allows for the evaluation of the severity of illness across resource settings to examine the role of critical illness or prolonged hospitalisation on symptoms and draw conclusions regarding causality between viral infection and neurological manifestations. A registry represents the ideal instrument for this purpose.

A registry as an instrument for a standardized data collection

Registries are the instruments used to detect and define the spectrum of a given disease in population-based samples or in specific settings. The demographic and clinical characteristics of the individuals to be included in a registry are pre-defined. The source(s) of cases is(are) identified. Each patient is assigned a unique identifier. The diagnosis, and any other factor deemed important for the description of a registered case, is defined using commonly accepted and unanimously applied criteria. The data are collected in compliance with these pre-assigned criteria. To preserve the representativeness of the sample, all patients eligible for inclusion and releasing an informed consent are registered. If a follow-up is required, patients are assessed at specific time points for the identification of any incident complication. Attrition can be minimized through an active and accurate search of the individuals qualifying for inclusion and, where a follow-up is needed, to be invited at follow-up visits.

Planning and development of a European registry

The EAN has been active since the start of the COVID-19 outbreak with a number of activities to promote knowledge, research and international collaborations [Moro et al, 2020]. Starting in April 2020, a Task Force was assembled, including clinicians and epidemiologists from various countries (the authors of the present report). One of the projects of this Task Force was to develop a European registry.

Objectives of a European COVID-19 registry

The overall aim of a European COVID-19 registry is to provide epidemiological data on the spectrum of neurological symptoms and signs in patients with COVID-19 infection reported by neurologists or other key referents in outpatient services, emergency rooms, or hospital departments. The registry can be implemented as a stand-alone instrument for patients with suspected or confirmed COVID-19 AND neurological findings or as *an addendum* to an existing registry not targeting neurologic signs and symptoms. More specific primary objectives are: 1. To evaluate the prevalence of neurological manifestations in patients with suspected or confirmed COVID 19 disease; 2. To assess the general characteristics of these neurological manifestations. Secondary objectives are: 1. To gain epidemiological data on neurologic manifestations of the COVID 19 infection in different countries in Europe and, where available, in non-European countries; 2. To study the impact of neurological symptoms and neurological complications on outcomes.

An accurate search was made of existing national registries and databases to identify the variables most commonly collected, with a threefold purpose: 1. To select the data considered of primary interest by most countries; 2. To favour data pooling and meta-analyses on common variables from differing sources;

3. To focus on variables that could be easily collected even in resource-poor countries. The variables identified were critically appraised and only those on which there was full agreement were retained. For each variable, a definition was provided resulting from widely accepted criteria or, where not available, fully agreed by the group. The collection of the data was kept to a minimum to prevent attrition and loss of data due to the constraints posed by the outbreak.

Patients to be registered

A patient was eligible for inclusion provided that all the following criteria were satisfied: 1. Age 18 or older; 2. Symptoms suggesting confirmed COVID-19 infection; 3. Case ascertainment through neurological consultation; 4. Patient's informed consent (according to the requirements of local regulatory agencies).

Study conduct

All neurologist members of the EAN or its affiliated national societies are entitled to participate and register all consecutive patients fulfilling the inclusion criteria they are asked to visit. No additional investigations were needed besides a detailed neurological examination and a list of the most common variables recorded in the pandemic. To expand the numbers of patients to be registered, data collection will be both prospective and retrospective. A number of general symptoms and signs of infection, a list of prominent comorbidities and a number of neurological diseases, selected among those identified in previous series and case-reports and accompanied by proper definitions, have been included in a semi-structured case report form (Table 1). All registered patients with neurological symptoms are asked to be followed for 12 months, with telephone calls at six and 12 months to verify the vital status, the functional abilities and identify neurological symptoms, signs or diagnoses that might have occurred after the acute phase of the disease. The neurologist (or a designated partner of the local study team) was required to be in charge of the follow-up.

Statistical analysis plan

Statistical analyses will be performed in conformity with two separate plans. The first plan refers to countries adhering to the EAN registry. The plan includes descriptive statistics to be performed on all variables collected in the registry. Inferential statistics are also included using conventional univariate and multivariate methods. Cross-tabulations were pre-planned to correlate each symptom, sign and neurological diagnosis to demographics and the other clinical variables, including comorbidities and the main complications of infection. These data will be presented in the entire sample and for each country separately. The neurological diagnoses made at the time of the infection will be contrasted to the status

at last observation (recovered, alive with functional impairment, dead). Multivariate analyses will be also performed using logistic regression models with status at last observation (alive/dead) as the dependent variable and neurological diagnoses as the independent variables, adjusting for demographics, comorbidities, setting and country. Follow-up data will be analysed in survivors with Kaplan-Meier curves using the occurrence of a neurological diagnosis as the outcome variable and demographics and comorbidities as prognostic predictors. Comparisons will be tested with the Log-rank test and independent prognostic predictors will be assessed using Cox's hazard models, adjusting for setting and country. Retrospective and prospective data will be analysed separately and compared. The modality for data collection (retrospective vs. prospective) will be also included in multivariable analysis models. The significance will be set at the 5% level (p=0.05).

A separate plan (still to be discussed with partners in charge of independent data collections and willing to share their data) will consider two options: 1. Inclusion of anonymized individual patient data; 2. A meta-analysis of aggregated data.

Sample size calculation

The primary endpoints of the EAN registry were to determine the prevalence of neurological manifestations in COVID-19 patients. The hypotheses tested by this registry are exploratory; hence a sample size calculation was not performed.

Implementation of the registry

When the protocol (Annex 1) and the case report form (Annex 2) were in final form, an extensive correspondence was started with the national societies affiliated to the EAN and with individual members. The goal was to advertise the registry and encourage countries and individuals to use this instrument. As of August 17 2020, a total of 254 centres from four continents declared their willingness to participate. A heatmap of the participating sites is illustrated in Fig.1. The profile of each centre will be provided through the completion of an ad-hoc form (Annex 3) that will also include the setting where the patient was registered.

While the EAN registry was distributed to the participating sites, a discussion was started with countries using their own registries in Europe with the intent to organise data sharing (individual patient data) or pooling (meta-analysis).

In parallel, an intensive collaboration was also started with the Global Consortium Study of Neurological Dysfunction in COVID 19 (GCS-NeuroCOVID), centrally coordinated through the University of Pittsburgh in

the United States. Endorsed by the Neurocritical Care Society (NCS) and the Neurocritical Care Research Network (NCRN), in end of March 2020 the GCS-NeuroCOVID investigators designed and implemented Tier-1, basic pragmatic cohort studies to determine neurological manifestations of COVID-19 and their prevalence among hospitalised COVID-19 patient population. This will be followed by Tier-2 study which will further characterise main phenotypes of neurological manifestations of COVID-19 along with evaluation of long-term outcome, and an experimental/translational Tier-3 study to investigate potential disease mechanisms and biomarkers [Needhan et al, 2020; Frontera et al, 2020]. The GCS-NeuroCOVID consortium also developed a paediatrics study arm to examine neurologic features of COVID-19 across the full lifespan. Currently, GCS-NeuroCOVID consortium has 123 adult and 96 paediatric sites representing all continents.

The similarities in scientific aims and the complimentary global outreach of the two large consortia (EAN and GCS-NeuroCOVID) generated an ideal opportunity for global collaboration. The two consortia plan to combine data in a general analysis which will provide important information on global and regional burden of neurological manifestations of COVID-19 pandemic. A Memorandum of Understanding (MOU) outlining terms of this collaboration was established and jointly signed by leaders of the EAN and the Neurocritical Care Society and the Neurocritical Care Research Network. This collaboration led to the planning of joint activities aimed at promoting harmonisation of data collection, to be extended to children and adolescents, and to include a more detailed search of data during follow-up.

At the same time, the World Health Organization (WHO) promoted a global forum aimed at identifying the most important issues to be investigated at a global level, in terms of improved knowledge of the spectrum of COVID-19 infection and its neurological acute and late complications, and the detection of failures in the provision of care. Representatives from both the EAN and the GCS-NeuroCOVID consortium investigators serve on this important mission.

Expected short-term and long-term findings

The activation of the EAN registry and its interaction with several other surveillance systems in and outside Europe will provide a number of short-term and long-term findings. In the short term, a more complete picture will be offered of the spectrum of the disease and its neurological complications, comparing the various settings where the patients were registered. The demographic and clinical profile of registered patients will be compared across European countries to detect similarities and differences. Demographic and clinical characteristics of patients from countries with differing proportions of affected individuals and COVID-related deaths will be also compared. Using the settings for denominators,

prevalence and incidence of neurological signs and diseases will be also calculated, separating the neurological manifestations of the infection from well-defined syndromic entities. Registered data will be also used to plan focused studies and the established registry can serve as a critical infrastructure to facilitate global research in future unanticipated events.

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Data availability statement: Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Figure 1. Map of Europe including the location of the centers participating in the EAN registry.

Annex 1. Study protocol.

Annex 2. Case report form.

Annex 3. Profile of participating center.

Table 1. List of variables included in the registry.

General & Demographic	Site of visit, Source of contagion, Results of testing (where available), Year of birth, Sex, Height, Weight, Smoking, Duration of infection
History	Arterial hypertension, Diabetes, Cardiovascular disease, Chronic kidney disease, Chronic liver disease, Chronic bronchial/pulmonary disease, Anemia, Cancer, Immune-mediated disease, Other non-neurological (specify), Neurological disease
General Covid-19 complications	Dyspnea, Pneumonia, Cardiovascular disease, Renal insufficiency/dialysis, Coagulation disorder/disseminated intravascular coagulopathy, Septic shock, Extracorporeal membrane oxygenation, Other (specify)
Admission	Hospital, Intensive Care Unit (mechanical ventilation)
New neurological manifestations	Date of onset, Headache, Hyposmia/hypogeusia, Dysautonomia, Vertigo, Myalgia, Sleep disturbances, Excessive daytime sleepiness/hypersomnia, Cognitive impairment, Dysexecutive syndrome, Hyperactive delirium, Hypoactive delirium/acute encephalopathy, Stupor/coma, Syncope, Seizures/status epilepticus, Meningitis/Encephalitis, Stroke, Movement disorders, Ataxia, Spinal cord disorder, Peripheral neuropathy, Other (specify)
Diagnostic tests	CSF, CT/MRI
Outcome	Modified Rankin Scale at discharge, If death, date, Autopsy
6-month follow-up	Modified Rankin Scale, New neurological manifestations, If death, date, Autopsy
12-month follow-up	Modified Rankin Scale, New neurological manifestations, If death, date, Autopsy

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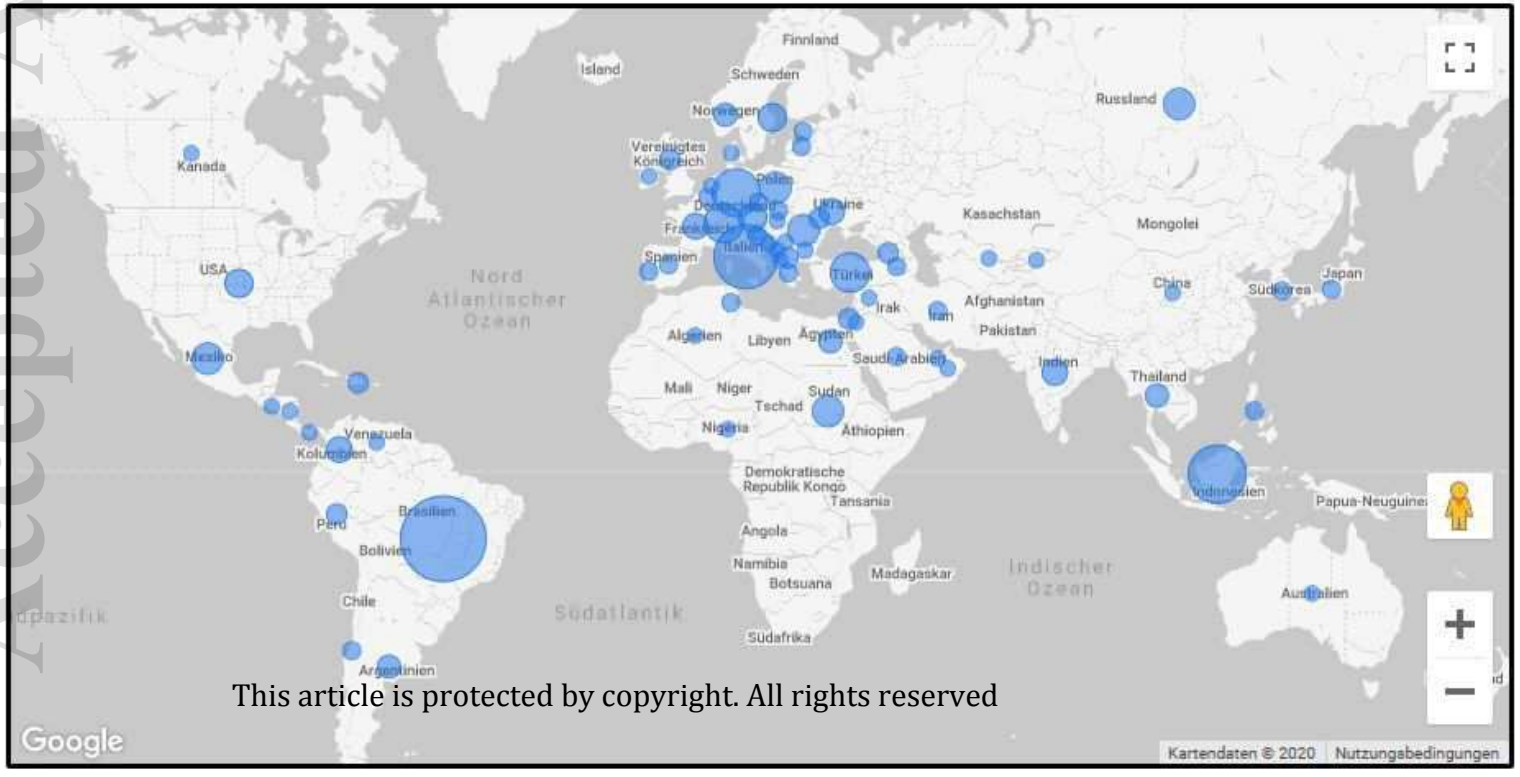
Registered Sites 265



	City	Country	Record Count
1.	Istanbul	Turkey	4
2.	Moscow	Russia	4
3.	Skopje	North Macedo...	3
4.	Tbilisi	Georgia	3
5.	Khartoum	Sudan	3
6.	Bucaramanga	Colombia	3
7.	Rio de Janeiro	Brazil	3
8.	Warsaw	Poland	2
9.	Rancagua	Chile	2
10.	Vila Velha	Brazil	2
11.	Oslo	Norway	2
12.	Bucharest	Romania	2
13.	Москва	Russia	2
14.	Guadalajara	Mexico	2
15.	Grenoble	France	2

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